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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,434	10/18/2005	Iwata Ozaki	1089.0580000/MAC	3772

26111 7590 06/08/2009

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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
06/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,434	OZAKI ET AL.	
	Examiner	Art Unit	
	LESLIE A. ROYDS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☒ Claim(s) *1,2,6,7 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *18October05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 are presented for examination.

Acknowledgement is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/JP04/06038, filed April 23, 2004, and Applicant's claim for benefit under 35 U.S.C. 119(a-d) to Japanese Patent Application No. 2003-118581, filed April 23, 2003, of which a certified copy was filed in the instant application October 18, 2005.

Applicant's Information Disclosure Statement (IDS) filed October 18, 2005 (two pages total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08(a-b), the Examiner has considered the cited references.

Objection to the Oath/Declaration

The oath or declaration is defective because the specification to which the oath or declaration is directed has not been adequately identified. Specifically, the declaration states, "The specification of which is attached hereto unless the following box is checked" and then provides information regarding the filing date of PCT Application No. PCT/JP04/06038 (wherein Applicant has stated in the Application Data Sheet (ADS) and p.1 of the specification that the instant application is a National Stage entry of this same PCT), but does not actually check the box indicating that the specification was previously filed with the PCT application. Accordingly, it would appear that Applicant intends to check the box at p.1 to indicate that the specification was previously filed, but since this box has not been checked, the declaration fails to adequately identify the specification to which it is directed. Correction is required. See MPEP §602. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by serial number and filing date is required. See MPEP §§ 602.01 and 602.02.

Objection to the Specification

The use of the trademarks KAYTWO capsules, GLAKAY capsules, KAYTWO syrup and KAYTWO N injection at p.6, l.11-15, have been noted in this application. Each letter of the trademark should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. Note that the above citation of trademarks is not necessarily an exhaustive list of each appearance in the instant specification. Accordingly, Applicant is requested to review the entire specification to correct all instances of said trademark(s) therein.

Objection to the Claims

Claim 1 is objected to for failing to define the acronym "MMP" at its first occurrence in the claims.

Claim 2 is objected to for failing to define the acronym "uPA" at its first occurrence in the claims.

Claim 6 is objected to for failing to define the acronym "AP-1" at its first occurrence in the claims.

Claim 7 is objected to for failing to define the acronym "Ets-1" at its first occurrence in the claims.

Claim 10 is objected to for failing to define the acronym "CDK" at its first occurrence in the claims.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode

contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In particular, the specification as originally filed fails to provide adequate written description for hydrates of menatetrenone (claims 1, 3-4 and 6-10).

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant's claims specify the use of hydrates of the instantly claimed menatetrenone compound, which is supported by the specification at p.5, l.15-20, which states, "The menatetrenone that is an active ingredient of the drug according to the present invention may be an anhydride or may form a hydrate.

There may be crystal polymorphism in the menatetrenone but this is not a limitation and the crystal form may be uniform or a mixture of multiple forms. Moreover, a metabolite produced by degradation of the menatetrenone of the present invention in vivo is also encompassed by the claims of the present invention."

Despite this disclosure, however, Applicant has failed to provide any structural characteristics, description of the form, such as, e.g., by describing the particular configuration, name(s), amount and structural arrangement of the water molecules, or physical properties, such as polarized light microscopy, single-crystal X-ray diffractometry, powder X-ray diffractometry, infrared spectroscopy, or the like, that would provide adequate written description of the hydrate forms of menatetrenone that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention. Accordingly, Applicant's disclosure, while noted, does not provide a teaching of what compounds other than menatetrenone *per se* recited in the specification (and salts thereof) would have been considered hydrate forms as presently claimed such that one of ordinary skill in the art would have been able to readily identify the scope of such hydrate forms that are functional to achieve the objectives instantly claimed.

In this regard, Vippagunta et al. ("Crystalline Solids", *Advanced Drug Delivery Reviews*, 48(2001):3-26, cited by Applicant) is cited for its teaching that, "The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition but different internal crystal structure and, therefore, *possess different physico-chemical properties*…Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color [12]. Differences in physical properties of various solid forms have an

important effect on the processing of drug substances into drug products [13], while differences in solubility may have implications on the absorption of the active drug from its dosage form [14], by affecting the dissolution rate and possibly the mass transport of the molecules…It is very important to control the crystal form of the drug during the various stages of drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a sold drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics [15]." (para. bridging col.2 of p.4 and col.1 of p.5) Note that a hydrate as claimed is a type of solvate.

This well-recognized irregularity in the form and function of drug hydrates must be taken into consideration when determining whether a disclosure provides sufficient written description for the genus of hydrate forms instantly claimed with at least a reasonable expectation that such forms would be functional to achieve the instantly claimed objective(s). The instant specification fails to provide any description of any specific hydrate forms that would fall within the claimed genus such that other members of the claimed genus could be immediately envisaged and/or readily identified. The idea that, in order to identify the other members of the genus, one of skill in the would have to undertake extensive hit or miss testing to determine the full scope of the genus is clearly indicative of the fact that Applicant was, in fact, *not* in possession of the full scope of hydrates claimed. This is because Applicant cannot logically be in possession of that which he has yet to identify.

While it may be construed that the fact that the hydrate form is similar to the chemical compound *per se*, but arranged via a different crystalline lattice structure, implies a similarity in chemical properties that would be sufficient to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to provide any description, such as, e.g., single crystal or powder X-ray diffraction patterns, of the ultimate structural characteristics of those hydrate forms that are

considered within the scope of those compounds intended for use by Applicant. Furthermore, as taught by Vippagunta et al., the physical and chemical properties of solvates and hydrates differ sufficiently that there would be no implication that the hydrates shared similar pharmacologic or chemical function. In the absence of such a description of the hydrate forms as presently claimed, Applicant's limitation to "hydrates" of the instantly claimed menatetrenone compound is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for all claim limitations must arise from either an explicit or an implicit suggestion by the disclosure to show that such a concept as now claimed was actually in possession of the Applicant at the time of the invention. For the reasons provided *supra*, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means that fully set forth the claimed invention, in such a way to reasonably convey to one skilled in the relevant art that Applicant had possession of the concept of employing hydrate forms of the menatetrenone compound presently claimed.

Accordingly, claims 1-10 fail to meet the requirements of 35 U.S.C. 112, first paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-5 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of cancer metastasis and invasion via treating cancer metastasis

and invasion using menatetrenone, does not reasonably provide enablement for (1) inhibiting cancer metastasis or invasion via preventing tumor metastasis using the same (claims 4-5) or (2) preventing cancer cell metastasis (claim 9). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The present rejection is made under the guidance of the MPEP at §2164.01(c), which states, "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)." Thus, the instant rejection made under 35 U.S.C. 112, first paragraph, is proper as it is applied to the present compound of claims 4-5 because such claims each specify the use of the compound for inhibiting cancer metastasis (specifically, hepatic cancer as recited in instant claim 5) and invasion.

For the purposes of consideration under 35 U.S.C. 112, first paragraph, it is noted that the term "inhibitor" circumscribes the aspect of prevention. Please see Merriam-Webster's Collegiate Dictionary

(Tenth Edition), which defines the term "inhibit" as "to prohibit from doing something" and further defines the term "prohibit" as "to prevent from doing something". In view of the fact that Applicant has not explicitly defined the term "inhibitor" to exclude such an aspect of prevention, the Examiner defers to the broadest, most reasonable interpretation consistent with the state of the art as described in MPEP §2111. As a result of the above citation to Merriam, the claims directed to an "inhibitor of cancer metastasis and invasion" (claims 4-5) are understood to also circumscribe the use of menatetrenone for the prevention of cancer metastasis and invasion.

The presently claimed invention is directed to an inhibitor of cancer metastasis and invasion comprising menatetrenone as the active ingredient, wherein the cancer may be hepatic cancer (claims 4-5). The presently claimed invention is also directed to a method for preventing cancer cell metastasis comprising administering an effective dose of menatetrenone or a pharmacologically acceptable salt thereof or a hydrate thereof in order to inhibit expression of MMP (claim 9).

In particular, one skilled in the art could not practice the presently claimed subject matter of inhibiting cancer metastasis or invasion via preventing cancer metastasis or invasion by administering an effective amount of menatetrenone without undue experimentation because the artisan would not accept on its face that prevention of cancer metastasis or invasion could actually be achieved given the state of the art at the time of the invention. Based upon the state of the art, as discussed below, and the evidence presented by Applicant, the artisan would have only accepted that the condition could be inhibited via the treatment of cancer metastasis with the compound as instantly claimed.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained*

therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe the use of the presently claimed compound menatetrenone for inhibiting cancer metastasis or invasion (claims 4-5) or preventing cancer cell metastasis (claim 9). That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed compound (i.e., menatetrenone) that cancer metastasis or invasion could be prevented. In other words, the skilled artisan would have understood the term "inhibiting" to circumscribe an aspect of "prevention" (see definitions *supra*) as required by instant claim 9 and, thus, would also have understood the present claims to allege that the claimed compound was capable of impeding the development or progression of cancer metastasis such that it would be "prevented", i.e., reasonably expected not to occur, in a host population treated via the instantly claimed compound. Because such preventive success is not reasonably possible with most diseases or disorders, especially conditions as complex, poorly understood and/or difficult to treat as cancer and its metastases, the specification, which lacks any direction or guidance as to how prevention of cancer metastasis could actually be achieved, is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding the prevention of cancer metastasis or invasion, the objective truth that such a condition could be prevented is doubted because the complex and poorly understood pathology of the condition, the obstacles and lack of effective therapies to treat tumors and metastatic conditions and the lack of preventive drugs for the same poses a significant challenge to achieving the objective of prevention of cancer metastasis.

In this regard, Burstein ("What's New is Metastasis Prediction and Prevention?", *Medscape,* May

2000:1-6) is cited. Burstein teaches, "For most patients with cancer, it is metastasis-the spread of cancer to distant organs-and not the primary tumor that proves to be life-threatening...The classic 'seed and soil' paradigm describes the principles of biology for metastatic cancer. Tumor cells must have acquired the ability to invade into normal tissues, enter the circulation, adhere to vascular tissues, penetrate into normal tissues, and prove viable in distant sites. In turn, the host environment must allow for tumor cell growth, with adequate blood supply and paracrine growth factors, for tumor cell survival. Thus, the clinical manifestation of metastatic disease will depend on specific changes in the tumor cells and specific environments within the body. These are multistep processes. Characteristics of the tumor cell and the host tissue environment can be targeted to alter tumor growth." (p.1)

Timar et al. ("Molecular Pathology of Tumor Metastasis III", *Pathology Oncology Research*, 9(1); 2003:49-72) is also cited and teaches that, "Therapy of tumor progression and the metastatic disease is the biggest challenge of clinical oncology. Discovery of the diverse molecule pathways behind this complex disease outlined an approach to better treatment strategies. The development of combined cytotoxic treatment protocols has produced promising results but no breakthrough in the clinical management of metastatic disease...Recently, advances in molecular cancer research have revealed numerous new therapeutic targets, some of which have already been tested in clinical settings...Despite a great deal of improvement in the control of loco-regional disease, only slow progress has been seen in systemic disease. As a result, mortality of cancer patients is still high due almost exclusively to the development of metastases...Since the process of metastasis is a complex interplay between the disseminating cancer cells and the host, rational and successful anti-metastatic interventions may target all of the participants of these interactions in which anti-proliferative/cytotoxic interventions are only parts of a much more complex approach." (abstract and "Introduction", p.49)

In light of such teachings, the circumstances of formulating effective and reasonable methods of prevention of cancer metastasis are highly complex and must take into consideration many factors,

including acquired drug resistance and ability to invade normal tissue, enter the circulation, adhere to vascular tissues and penetrate into normal tissues, establish viability in distant sites, infiltrate an environment that allows for tumor cell growth with adequate blood supply and paracrine growth factors for tumor cell survival, etc. Given the underdeveloped state of the art with regard to the prevention of cancer metastasis, which recognized the complex pathogenesis of metastatic cancer and the inability to form effective therapies to prevent the systemic spread and metastases associated with cancer due to the complexity of the physiological interactions and molecular pathways that contribute to the metastatic spread of the disease, one of ordinary skill in the art would not accept on its face Applicant's statement that the development of cancer metastasis could be effectively inhibited (i.e., prevented) or prevented without placing a burden of undue experimentation upon the skilled artisan to determine how such an objective could actually be achieved. Such success would not have been reasonably expected in light of what is presently disclosed because the art at the time of the invention failed to recognize any effective methods of preventing cancer metastasis and Applicant has failed to provide any guidance as to who such an objective for administering a pharmacologic therapy with the outcome of preventing cancer metastasis could actually be achieved. Accordingly, the present specification fails to enable the full scope of this invention as it related to the objective of inhibiting (i.e., preventing) or preventing cancer metastasis from developing or progressing and, thus, fails to rebut the presumption of unpredictability in the art with regard to this same objective.

It is clear from the discussion above that the state of the art with regard to the prevention of cancer metastasis is highly unpredictable. The amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification requires more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re Fisher*, 427 F.2d 833, 839,

166 USPQ 18, 24 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.,* 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant provides various studies of the instantly claimed menatetrenone compound and its ability to, *inter alia*, reduce cancer cell proliferation in various cancer cell lines (p.7), its effect on cell cycle regulator genes, including cyclin dependent kinase inhibitors p21, p16 and p27 (p.7-8), its ability to reduce cancer cell metastasis, reduction in MMP expression, etc. (p.8-11). Please see, e.g., the Examples at p.7-13 of the instant specification. However, none of these studies demonstrate the ability of the claimed menatetrenone compound to effectively prevent cancer metastasis from developing or progressing. While a lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed compound for achieving the objective of inhibiting (i.e., preventing) cancer metastasis or invasion or preventing cancer cell metastasis from developing or progressing. Nowhere does the specification disclose the manner or procedure of using the presently

claimed menatetrenone compound for inhibiting cancer metastasis or invasion or preventing cancer cell metastasis such that the skilled artisan would have been imbued with at least a reasonable expectation of success in effectively preventing such a condition in a host or subject without the burden of an undue level of experimentation.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method or using the claimed product in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the objective of (1) inhibiting cancer metastasis or invasion via the prevention of cancer metastasis (claims 4-5) or (2) preventing cancer cell metastasis (claim 9) using an effective amount of menatetrenone could be achieved. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse by the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Ida et al. (U.S. Patent No. 5,021,570; 1991).

Ida et al. teaches an aqueous solution containing fat-soluble vitamin K prepared by adding, to an aqueous solution containing menatetrenone (vitamin K_2) and hydrogenated lecithin, the following: vegetable oil(s), glycerol fatty acid ester(s) or sorbitan fatty acid ester(s) in an amount of 0.004-5% by weight based on the whole aqueous solution (col.1, l.53-60).

Applicant recites limitations directed to the function of the claimed menatetrenone compound as (1) an MMP expression inhibitor (claim 1), particularly MMP-1, MMP-3, MMP-7 or MMP-14 (claim 2); (2) a uPA expression inhibitor (claim 3); (3) an inhibitor of cancer metastasis and invasion (claim 4), particularly when the cancer is hepatic cancer (claim 5); (4) an AP-1 activity inhibitor (claim 6); (5) an Ets-1 expression inhibitor (claim 7); (6) a prognosis improver for cancer therapy (claim 8); or (7) an expression promoter for CDK inhibitor p16, p21 or p27 (claim 10), which are met by the teachings of Ida et al. because the composition of Ida et al. comprises the identical active agent (i.e., menatetrenone, also known as vitamin K_2) to that instantly claimed. Therefore, the menatetrenone composition of Ida et al. must necessarily possess these same functions and properties as that presently claimed, whether recognized by the patentee or not, because products of identical chemical composition cannot have mutually exclusive properties. In other words, if the prior art teaches the identical chemical and physical structure of the composition (i.e., same active agent, etc.), then the properties that Applicant discloses and/or claims must necessarily be present. See MPEP §2112. Applicant is further reminded that, if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation

and is of no significance to claim construction. See *Pitney Bowes, Inc. v. Hewlett-Packard Co.*., 182 F.2d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 378, 42 USPQ2d 1550, 1554 and MPEP §2112.02(II).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ida et al. (U.S. Patent No. 5,021,570; 1991) in view of Remington's Pharmaceutical Sciences (1980; p.420-425).

Ida et al. teaches an aqueous solution containing fat-soluble vitamin K prepared by adding, to an aqueous solution containing menatetrenone (vitamin K_2) and hydrogenated lecithin, the following: vegetable oil(s), glycerol fatty acid ester(s) or sorbitan fatty acid ester(s) in an amount of 0.004-5% by weight based on the whole aqueous solution (col.1, l.53-60).

Applicant recites limitations directed to the function of the claimed menatetrenone compound as (1) an MMP expression inhibitor (claim 1), particularly MMP-1, MMP-3, MMP-7 or MMP-14 (claim 2);

(2) a uPA expression inhibitor (claim 3); (3) an inhibitor of cancer metastasis and invasion (claim 4), particularly when the cancer is hepatic cancer (claim 5); (4) an AP-1 activity inhibitor (claim 6); (5) an Ets-1 expression inhibitor (claim 7); (6) a prognosis improver for cancer therapy (claim 8); or (7) an expression promoter for CDK inhibitor p16, p21 or p27 (claim 10), which are met by the teachings of Ida et al. because the composition of Ida et al. comprises the identical active agent (i.e., menatetrenone, also known as vitamin K_2) to that instantly claimed. Therefore, the menatetrenone composition of Ida et al. must necessarily possess these same functions and properties as that presently claimed, whether recognized by the patentee or not, because products of identical chemical composition cannot have mutually exclusive properties. In other words, if the prior art teaches the identical chemical and physical structure of the composition (i.e., same active agent, etc.), then the properties that Applicant discloses and/or claims must necessarily be present. See MPEP §2112. Applicant is further reminded that, if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. See *Pitney Bowes, Inc. v. Hewlett-Packard Co.*,, 182 F.2d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 378, 42 USPQ2d 1550, 1554 and MPEP §2112.02(II).

Ida et al. fails to teach the use of pharmaceutically acceptable salts of menatetrenone (claims 1, 3-4, 6-8 and 10).

The use of pharmaceutically acceptable salts of the same would have been a matter well within the purview of, and *prima facie* obvious to, the skilled artisan because, as taught by Remington's Pharmaceutical Sciences, drugs may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (col.2,

p.424, para.1). Thus, it would have been *prima facie* obvious to the skilled artisan motivated by any one or more of these factors to formulate the disclosed menatetrenone compound of Ida et al. into a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form would have been the same or substantially similar to that of the agent itself.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 9 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,138,433 in view of Merriam-Webster's Dictionary (1996, p.601 and 932).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the cited application are not considerably patentably distinct from each other because the pending claims are anticipated by the patented claims.

The patented claims clearly provide for a method directed to the inhibition of the recurrence of hepatocellular carcinoma, comprising administering an effective dose of a medicine containing menatetrenone to a patient who had hepatocellular carcinoma and was subjected to treatment of hepatocellular carcinoma in the past.

Though the patented claims do not specifically recite the "prevention" of hepatocellular carcinoma recurrence, it is noted that the term "inhibit" circumscribes the aspect of prevention. Please see Merriam-Webster's Collegiate Dictionary (Tenth Edition), which defines the term "inhibit" as "to prohibit from doing something" and further defines the term "prohibit" as "to prevent from doing something". See p.601 and 932. In view of the fact that Applicant has not explicitly defined the term "inhibitor" to exclude such an aspect of prevention, the Examiner defers to the broadest, most reasonable interpretation consistent with the state of the art as described in MPEP §2111. As a result of the above citation to Merriam, the claims directed to inhibiting the recurrence of hepatocellular carcinoma (patented claim 1) are understood to also circumscribe the prevention of hepatocellular recurrence.

Note also that, while the patented claims are not explicitly directed to metastasis of hepatocellular carcinoma, the very teaching of "recurrence" is understood to circumscribe a recurrence of the hepatocellular carcinoma both at the primary site (non-metastatic), as well as secondary sites (metastases). However, even if, *arguendo*, the patented claims were interpreted not to circumscribe recurrence at both the primary site and a secondary site, it is noted that the very teachings of the administration of the identical compound (i.e., menatetrenone) to that presently claimed in the same host or subject (i.e., a patient with hepatocellular carcinoma; note that the instant claims may be practiced in any host or subject), must necessarily possess the same effects on cancer metastasis, even though such a property may not have been explicitly appreciated by the patentee at the time of the invention. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host using the same amount. See MPEP §2112.

Accordingly, rejection of claim 9 is proper over claims 1-4 of U.S. Patent No. 7,138,433 as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 1-10 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE A. ROYDS whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

June 4, 2009